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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

[Docket No. 1998D–0834]

Draft Guidance for Industry on Labeling for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Prescribing Information for Health Care Providers and Patient Labeling; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Prescribing Information for Health Care Providers and Patient Labeling." The draft guidance is intended to assist applicants in developing labeling for new drug applications (NDAs) for such drug products. This is the third draft of the guidance, which initially issued in September 1999.

DATES: Submit written or electronic comments on the draft guidance by [*insert date 60 days after date of publication in the* **Federal Register**]. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing

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your requests. Submit written comments on the draft guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Margaret Kober, Center for Drug Evaluation and Research (HFD–580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4243.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Prescribing Information for Health Care Providers and Patient Labeling." The draft guidance describes the recommended labeling for health care providers and patient instructions for inclusion in NDAs. A draft of this guidance was first issued on September 27, 1999 (64 FR 52100). However, on September 10, 2002, the agency withdrew the draft guidance (67 FR 57432), pending consideration of the results from the National Institutes of Health (NIH) Women's Health Initiative (WHI). In the **Federal Register** of February 3, 2003 (68 FR 5300), the agency issued a second draft reflecting the agency's thinking after considering the results of the WHI substudy concerning overall risks and benefits of hormone therapy for postmenopausal symptoms.

The agency is issuing this third draft guidance to address comments received, to incorporate new study results from the WHI, and to better inform prescribers and patients regarding the availability of the lowest effective dose

for these drug products. This third draft supersedes the second draft and reflects the agency's thinking after considering these issues. Further revisions to the guidance may be necessary as additional information becomes available.

On May 31, 2002, the WHI study of conjugated estrogens 0.625 milligram (mg)/day (CE) plus medroxyprogesterone acetate 2.5 mg/day (MPA) in postmenopausal women was stopped after a mean of 5.2 years of followup because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. Data on the major clinical outcomes through April 30, 2002, regarding increased risks for invasive breast cancer, heart attacks, strokes, and venous thromboembolism rates, including pulmonary embolism, became available July 17, 2002. On March 17, 2003, additional information was published about health-related quality of life.

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, was published on May 28, 2003. It concluded that women treated in the study with conjugated estrogens 0.625 mg combined with medroxyprogesterone acetate 2.5 mg have a greater risk of developing probable dementia than those on placebo. Detailed information about WHIMS is available at *http://www.nih.gov/PHTindex.htm.*

This third draft of the guidance retains and updates the labeling recommendations regarding the results of the WHI study and recommends adding risk information related to the results of the WHIMS study to appropriate sections of the labeling, including the boxed warning. It also adds to the WARNINGS section that use of estrogen-containing products may increase the risk of mammographic abnormalities. In addition, because it is unknown whether risks for postmenopausal women prescribed estrogen-

containing products for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy differ depending on the dose prescribed, the guidance recommends that labeling include a statement as to whether or not the lowest effective dose for the product has been identified.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on labeling for noncontraceptive estrogen drug products for the treatment of moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the draft guidance. Two copies of mailed comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either *http://www.fda.gov/cder/guidance/index.htm* or *http://www.fda.gov/ohrms/dockets/default.htm.*

Dated: 2/9/04
February 9, 2004.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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